Hemodiafiltration and CKD-MBD

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Chronic Kidney Disease-Mineral and Bone Disorder CKD-MBD

Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD)

- Abnormal Ca, PO4, PTH and Vitamin D metabolism
- Abnormal bone turnover, mineralisation and growth
- Calcification of the cardiovascular system and soft tissue

KDIGO, KI 2006

CKD-MBD

Classification

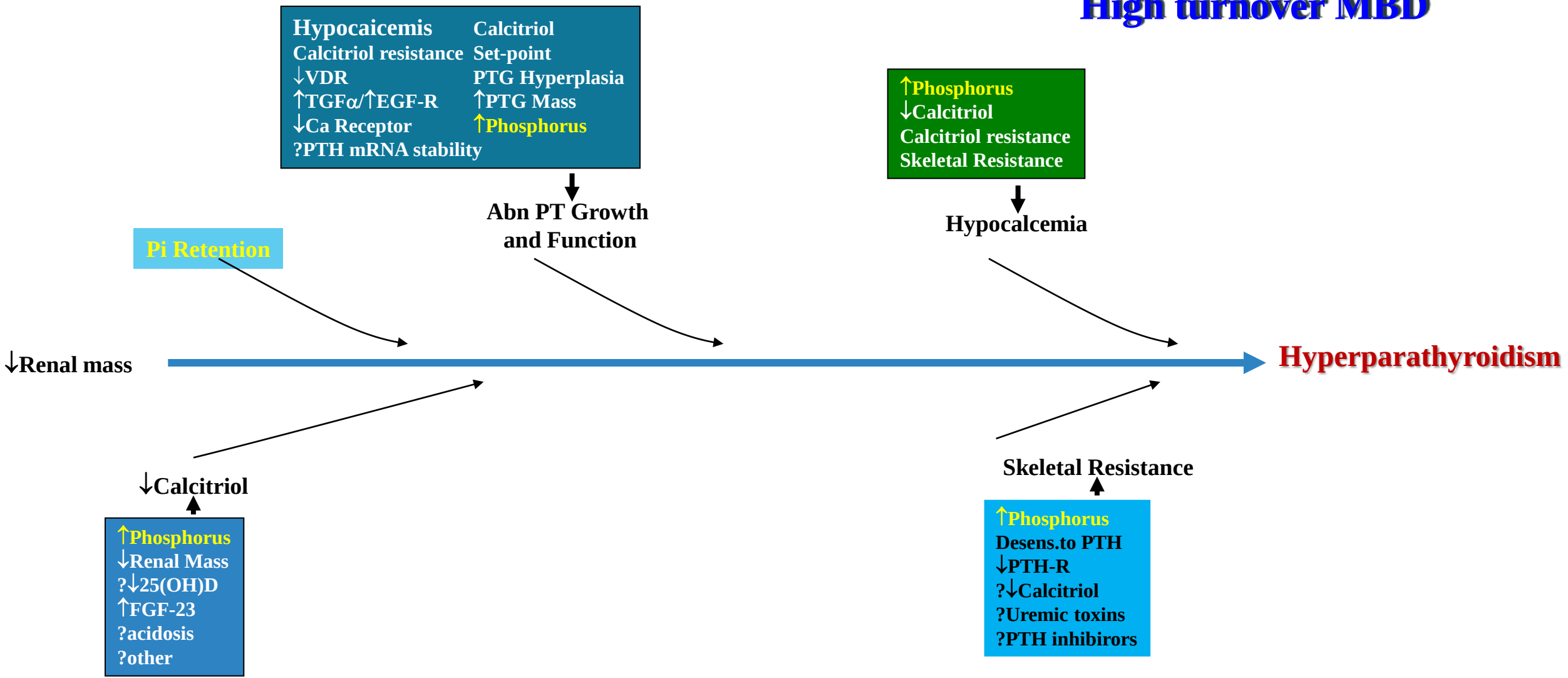
Renal Osteodystrophy

Type	Laboratory Abnormalities	Bone disease	Calcification of vascular or other soft tissue
L	+	-	-
LB	+	+	-
LC	+	-	+
LBC	+	+	+

CKD-MBD

Pathogenesis

High turnover MBD



Serum Phosphorus and Vascular Calcification

Consequences of hyperphosphatemia and elevated levels of the calcium–phosphorus product in dialysis patients

Nathan W. Levin and Nicholas A. Hoenich

Control of serum phosphorus levels is a central goal in the management of patients with chronic renal failure. Inadequate control of serum phosphorus leads to elevated levels of the calcium–phosphorus product. This plays a pivotal role in vascular calcification, cardiovascular disease, calciphylaxis, and death. Elevated phosphorus and elevated levels of the calcium–

Introduction

In early renal failure, the serum phosphorus concentration is maintained in the normal range by an increase in plasma parathyroid hormone (PTH). As renal function declines, hyperphosphatemia becomes increasingly common. For patients receiving regular dialysis for end-stage

Elevated serum phosphorus levels and elevated levels of calcium-phosphorus product has been implicated as a major factor in the development of tissue and arterial calcification and cardiovascular disease.

Curr Opin Nephrol Hypertens 10:563±56 8. 2001 Lippincott Williams & Wilkins.

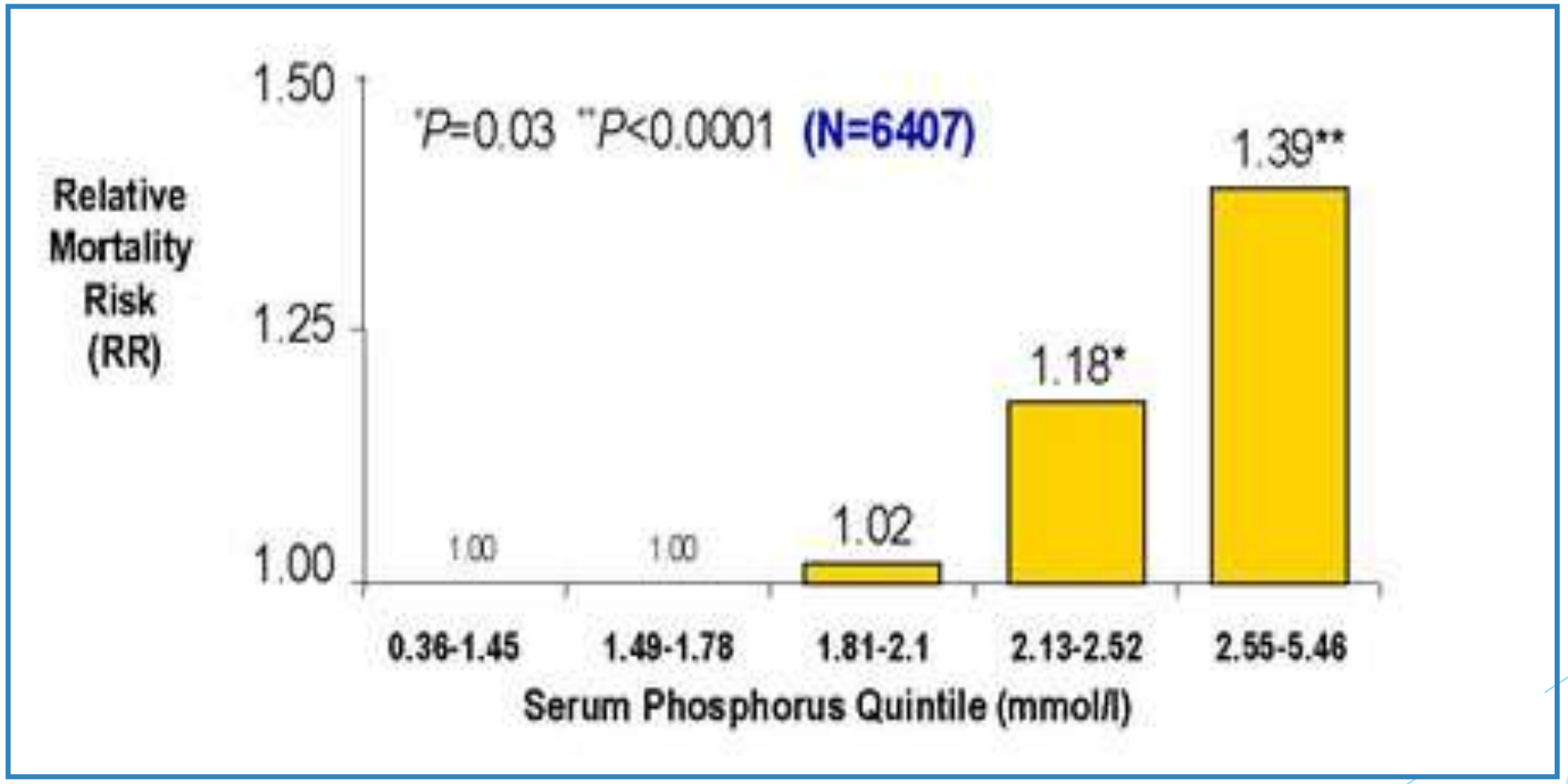
Serum Phosphorus and Vascular Calcification

Pediatric studies of surrogate markers of vascular abnormalities

	No of patients	Ca x P	P binders	P	Vit D	PTH
Litwin, 2000 CIMT	37	Y	Y		Y	
Mitsnefes, 2005 CIMT/stiffness LVM	16	Y	Y Y	Y Y	Y Y	Y Y
Civilibal, 2006 CAC	39	Y	Y	Y	Y	Y
Ruiz, 2007 CAC	4				Y	
Shroff, 2007 CAC CIMT	85			Y Y	Y Y	Y Y

Serum Phosphorus and Mortality

Elevated serum phosphate increases mortality risk

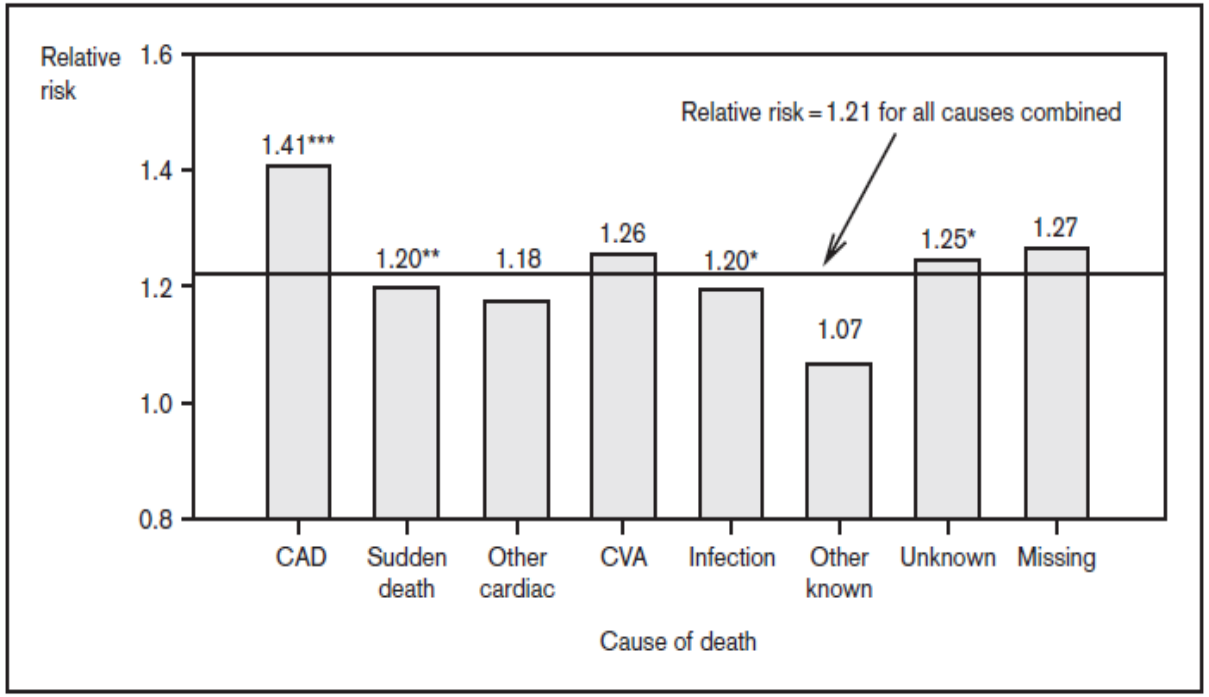


The mortality rate increases by 6% for each 0.3mmol/L rise in phosphorus levels

Serum Phosphorus and Mortality

Figure 1. Adjusted relative risk of mortality by cause of death for patients with serum phosphate levels above 6.5 mg/dl compared with that for patients with serum phosphate levels of 2.4–6.5 mg/dl

*$P<0.05$, compared with a relative risk of 1.0; **$P<0.001$, compared with a relative risk of 1.0; ***$P<0.0005$, compared with a relative risk of 1.0. CAD, coronary artery disease; CVA, cerebrovascular accident. Reproduced with permission from [2].



Ganesh SK, Stack AG, Levin NW, et al. Association of elevated serum PO4, Ca6PO4 product and PTH with cardiac mortality risk in chronic hemodialysis patients. Am J Kidney Dis

Hyperphosphatemia is an INVISIBLE THIEF

Mortality

Hyperphosphatemia Control

Phosphate binders

Diet

Dialysis

Does Conventional HD Provide Adequate Phosphate Control?

- Almost 50% of hemodialysis (HD) patients have phosphate levels greater than recommended treatment targets despite the use of phosphate lowering agents and dietary recommendations.
- Children treated by conventional dialysis regime still have an increased risk of cardiovascular morbidity.

No

Groothoff et al. Kidney Int. 2002; 61:621–629.
Foley et al. J Am Soc Nephrol. 1998; 9:S16–S23.

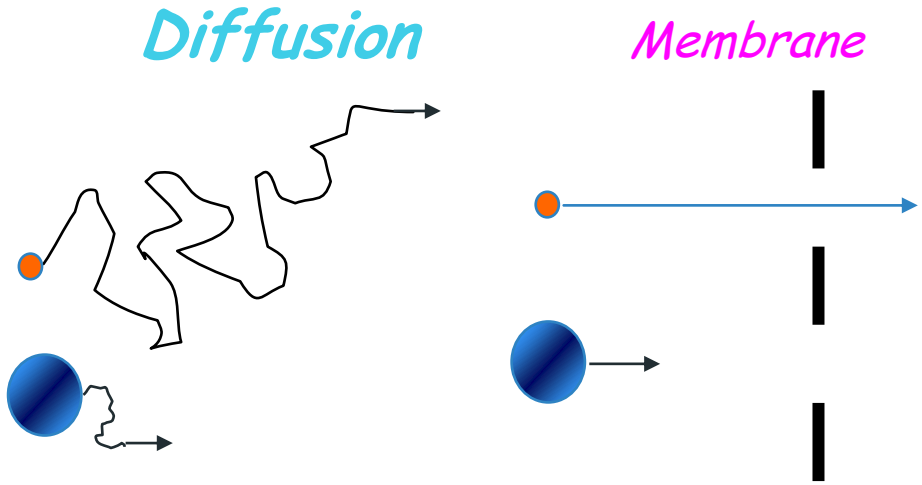
Why Does Not Conventional HD Provide Adequate Phosphate Control?

Solute Transport in Hemodialysis

- **Diffusive transport of solutes**

  Relevant:- cut-off of membrane

  - weight of solutes

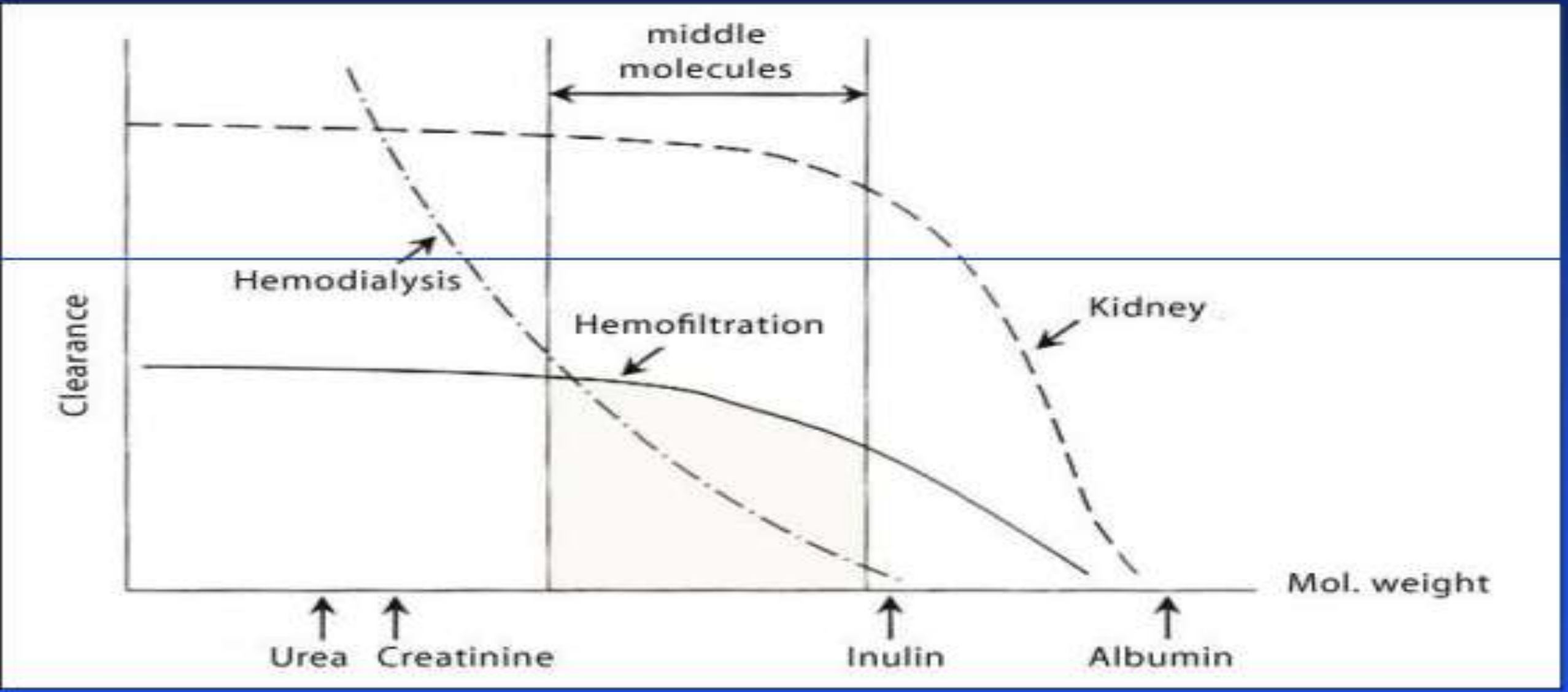


Solute Transport in Hemodialysis

Types of solutes

- Low-molecular-weight (MW) toxins (MW <500 D)
- Middle-MW toxins (500 to 15,000 D), referred to collectively as middle molecules (MMs)
- Large solutes (>15,000 D), frequently classified as large-molecular-weight proteins (LMWPs)

Solute fluxes in different treatment modalities



Solute Transport in Hemodialysis

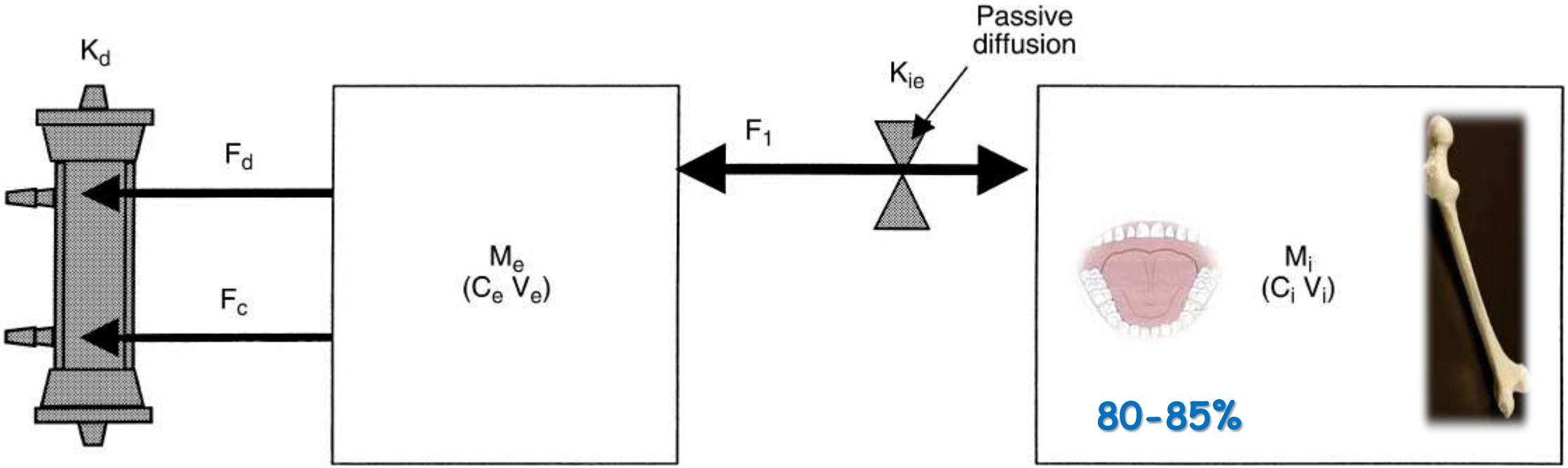
Small Water Soluble Molecules (MW <500 Daltons)	Middle Molecules (MW >500 Daltons)	Protein-Bound Molecules (MW >500 Daltons)*
Sodium (23)	Adrenomedullin (6032) (potent hypotensive peptide)	Hippuric acid (insulin resistance and glucose intolerance)
Phosphorus (31)	AGE*	Homocystein (atherogenecity and thrombogenecity)
Potassium (35)	AOP*	Indoxyl sulfate (pro-inflammatory effect & endothelial dysfunction)
Urea (60)	Vitamin B12 (1355)	- *p*-cresylsulfate – *p*-cresol (endothelial and pro-inflammatory)
Creatinine (113)	Endothelin (4238) (strong vasoconstrictor)	Polyamines (inhibit erythroid colony growth in a dose-dependent way)
Uric acid (168)	PTH (9225)	
Glucose (180)	β_2-M (11800)	
	Leptin (16000)	
	Cytokines (15000-30000)	
	Immunoglobulin LC (28000 – 56000 Da)	
	Uridine adenosine tetraphosphate (very strong vasoconstrictive)	

Table 1. Examples of types and sizes of different uremic toxic molecules.

Why Does Not Conventional HD Provide Adequate Phosphate Control?

Phosphate Kinetics During Hemodialysis

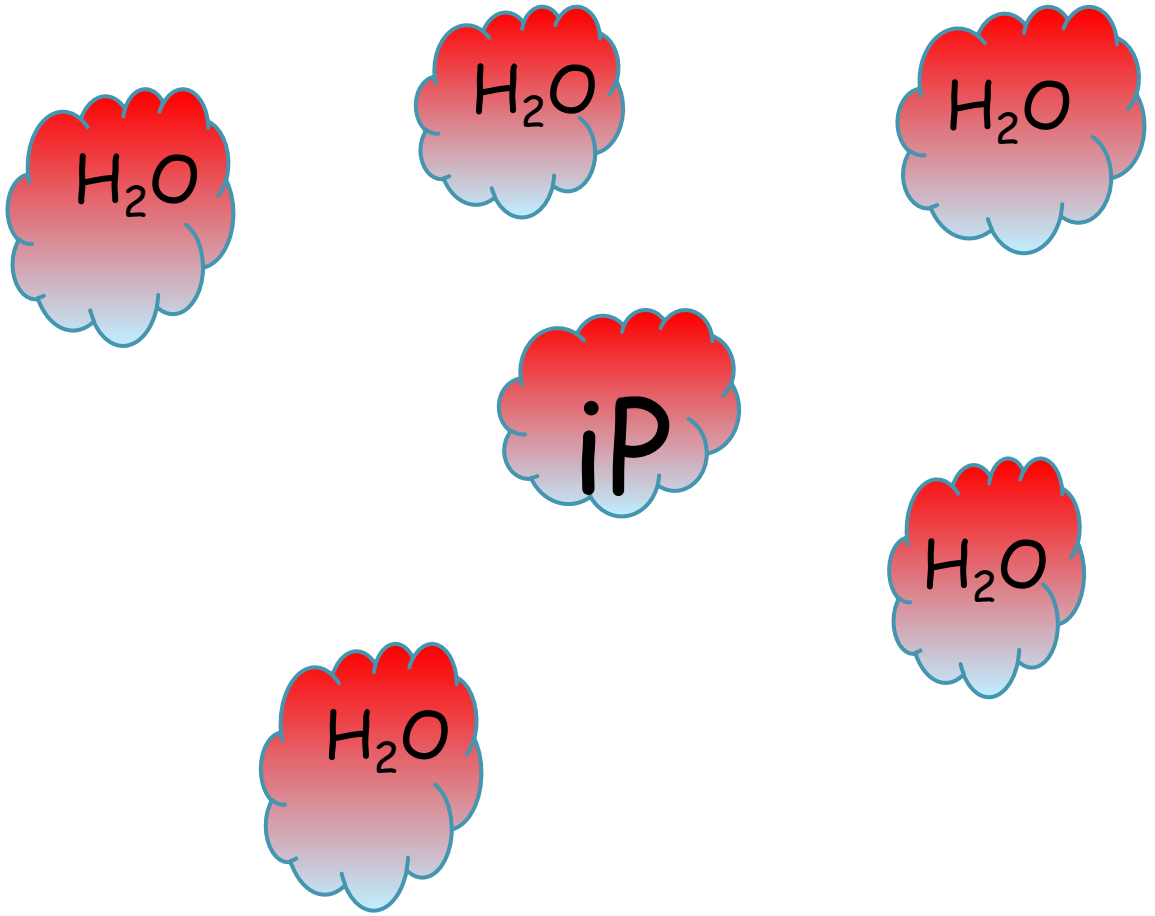
1. Slow and difficult post dialysis rebound



Spalding et al. Kidney Int. 2002;61(2):655-667.

Phosphate Kinetics During Hemodialysis

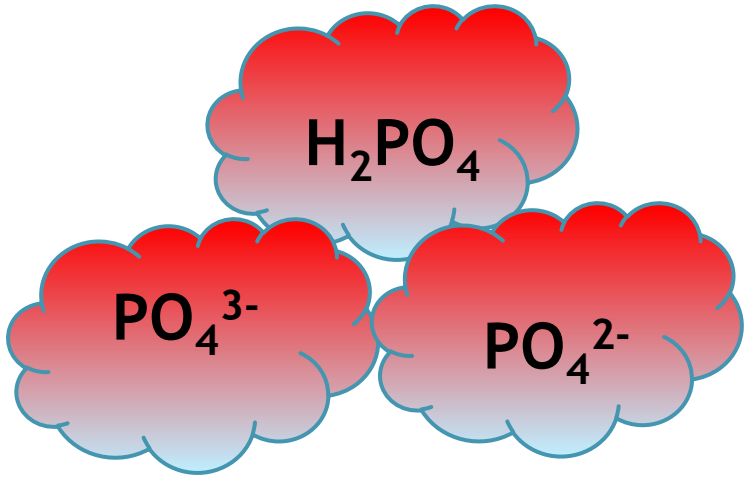
2. Change of small-sized mole into medium-sized mole



Pribil et al. *J Comput Chem*. 2008;29(14):2330–2334.
Ety al. *Phys Chem Chem Phys*. 2003;5: 4686–4690.

Phosphate Kinetics During Hemodialysis

3. Increased negative charge of hydrated P ions



Pribil et al. *J Comput Chem*. 2008;29(14):2330–2334.
Ety al. *Phys Chem Chem Phys*. 2003;5: 4686–4690.

But Looks Sometimes Can Be Deceiving ….

Although P is a small-sized mole it behaves as medium-sized mole

Phosphate Kinetics During Hemodialysis

- Attempts to improve phosphate clearances by increasing dialyzer surface area, switching dialyzer from low to high flux, using higher blood flow and dialysate flow have either been reported to have no effect or a variable effect.

Phosphate Kinetics During Hemodialysis

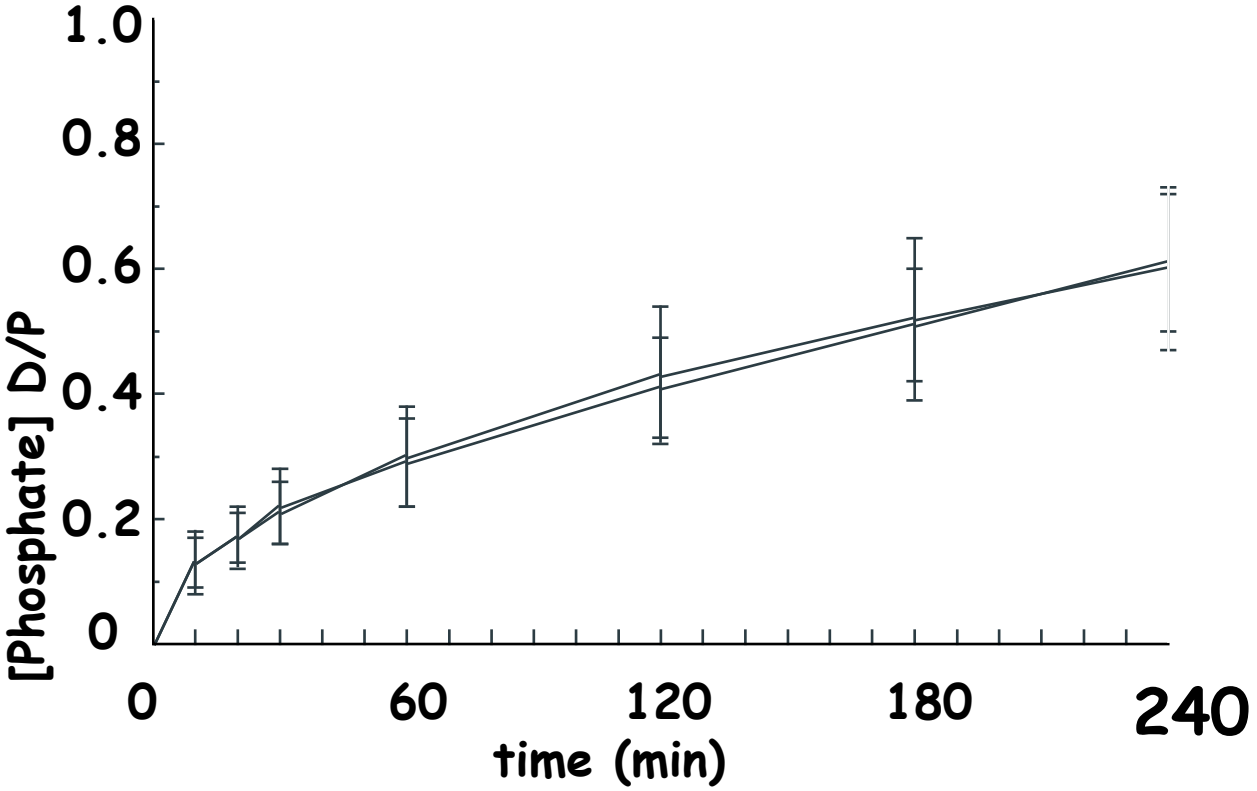


Table 1 Ranges of phosphate removal (grams per week) by different dialysis strategies

Conventional diffusive hemodialysis, 4 hours	2.3–2.6 g
Extended diffusive hemodialysis, ≥5 hours	3.0–3.6 g
Nocturnal hemodialysis, ~8 hours	4.5–4.9 g

International Journal of Nephrology and Renovascular Disease 2013:6

Hyperphosphatemia, which has been associated with vascular calcification and considered as an independent predictor of mortality in dialysis patients, has been well controlled with efficient removal of phosphorus by online HDF with marked reduction in phosphate binders

Does HDF Provide Adequate Phosphate Control?

Hemofiltration

- Larger size uremic toxins can be dragged and removed from blood by filtering large volume of fluid pushed under high hydrostatic pressure(Convection) through a larger pore size membrane (high cut-off membrane/high-flux dialyzer).
- Fluid balance is maintained by infusion of replacement solutions, administered before filter (pre-dilution) or after the filter (post-dilution) to replace the large volume of filtered fluids (convection volume).

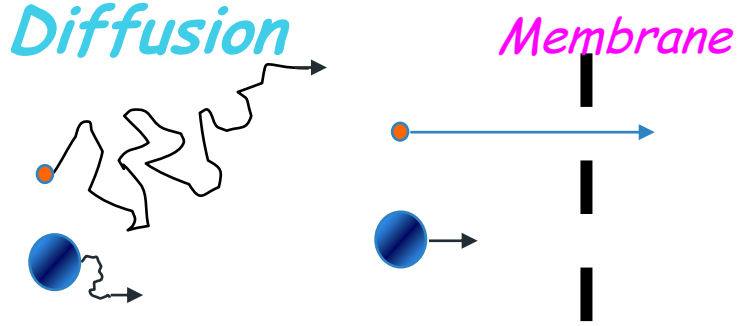
Hemodiafiltration

- Combination of the two physiologic principles of diffusion (hemodialysis) and convection (hemofiltration) in the management of patients with ESRD is known as "hemodiafiltration" a technique that has been described and implemented in 1974 and a treatment modality that simulate to a large extent the natural function of a normal kidney.
- Hemodiafiltration (HDF) is the blood purification therapy choice for those who want significant removal of uraemic solutes beyond the traditional range of small molecules.

Solute Transport in Different Dialysis Modalities

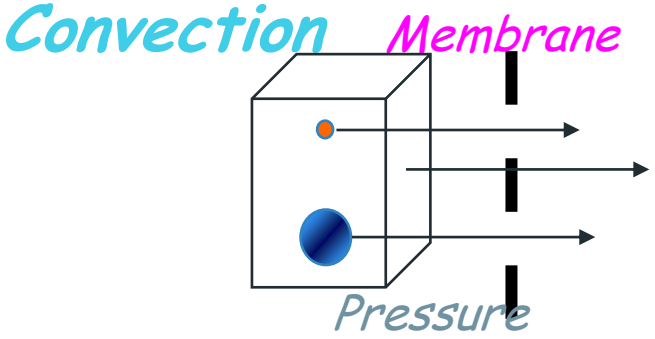
- ***Hemodialysis:***
  - *Diffusive transport of solutes*

    Relevant: - cut-off of membrane
    - weight of solutes



- ***Hemofiltration***
  - *Convective transport of solutes*

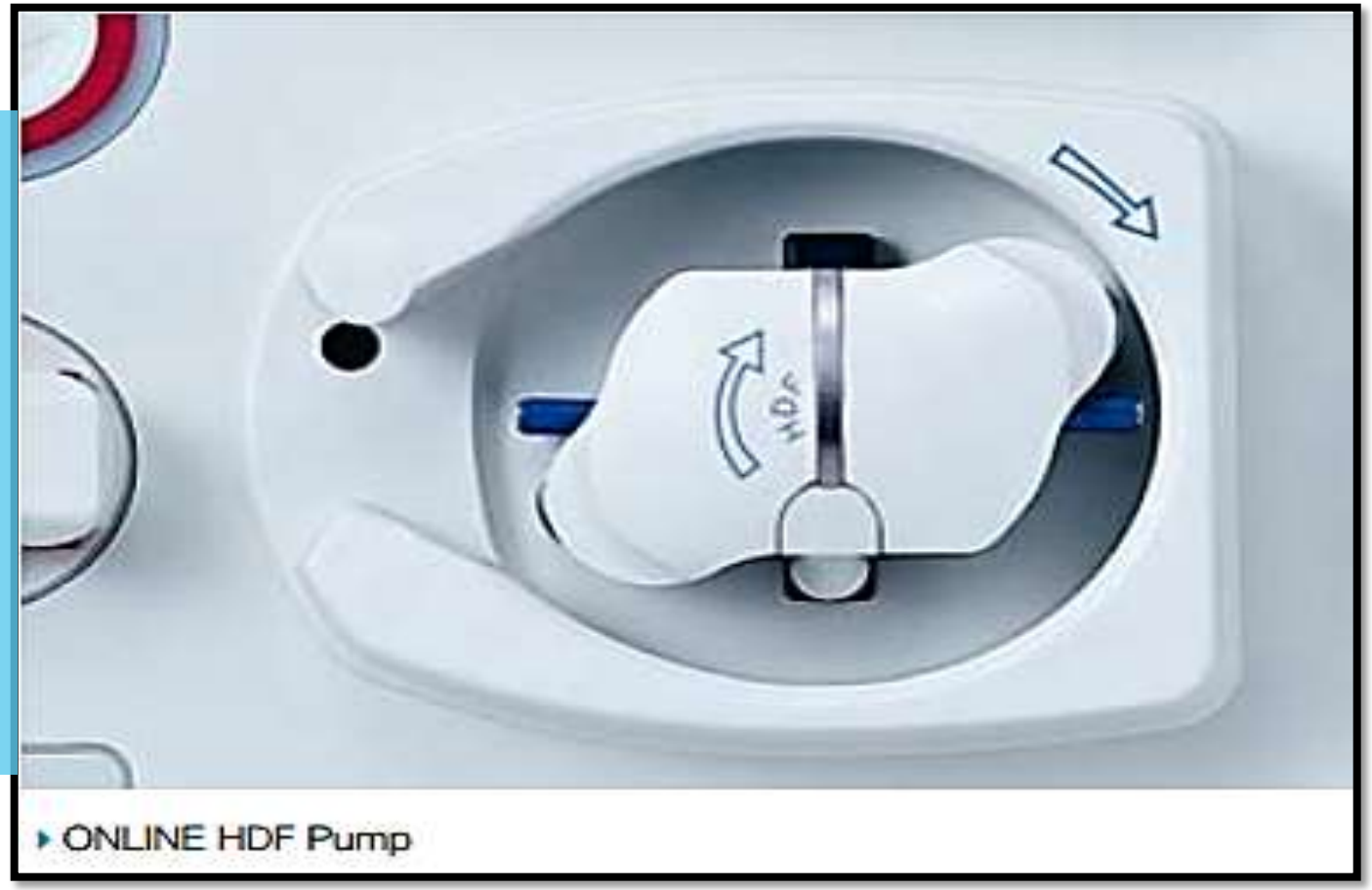
    Relevant: - cut-off of membrane
    - flow across membrane



- ***Hemodiafiltration***
  - ***Diffusive transport of small solutes***
  - ***Convective transport of large solutes***

ONLINE Hemodiafiltration is Now Recognised as the most Advanced Hemodialysis Treatment Modality

HDF was first introduced in adults in 1974, children 1982.



Does HDF Provide Adequate Phosphate Control?

Yes

Several studies have proved the superiority of HDF over conventional hemodialysis in clearance of phosphate.

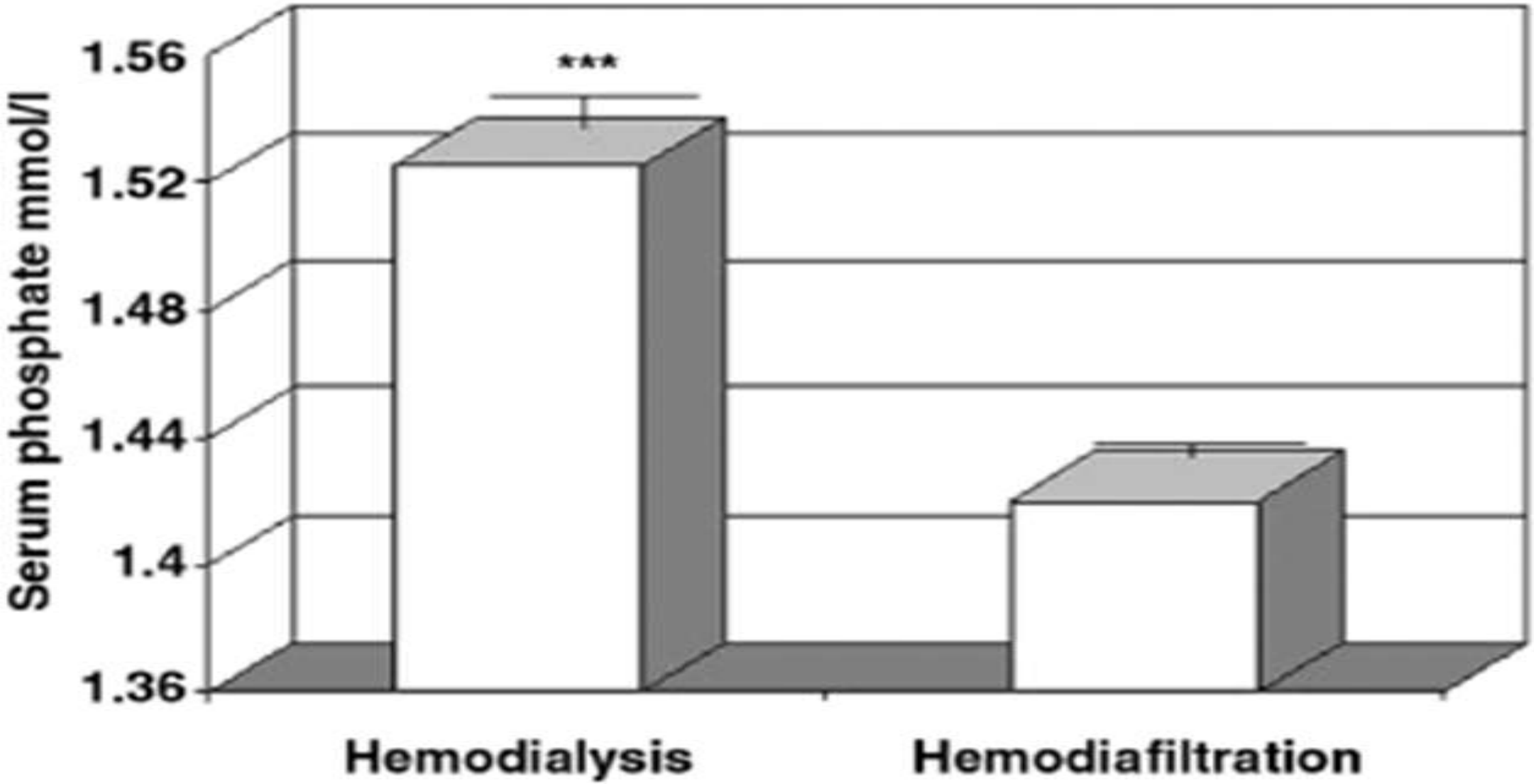


Fig. 1. Serum phosphate in hemodialysis and hemodiafiltration cohorts. Data expressed as mean (SEM). ***$P < 0.001$.

Penne et al

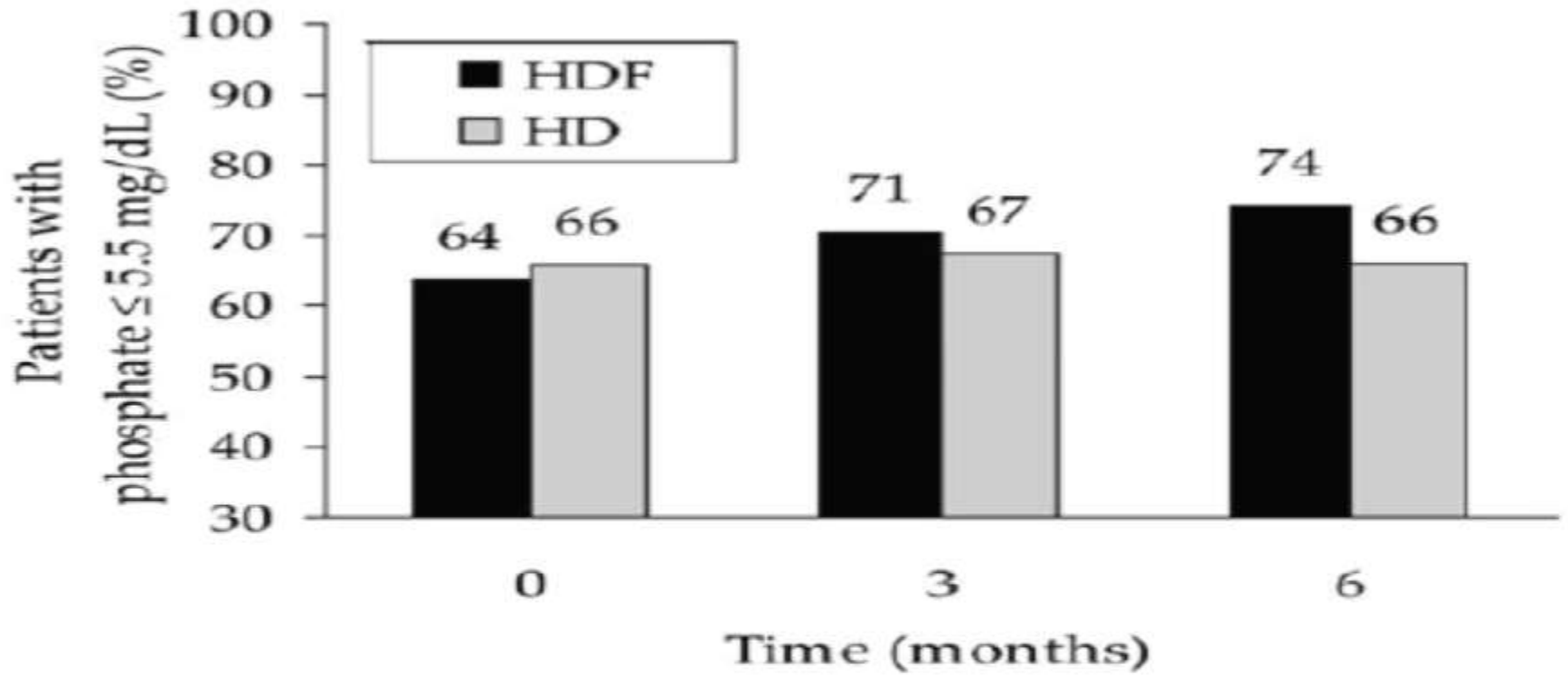


Figure 3. Proportion of patients achieving phosphate treatment targets at baseline and after 3 or 6 months of follow-up. Numbers above bars represent percentages. [a]$P < 0.05$ (vs baseline); [b]$P < 0.05$ (difference in change between groups). Abbreviations: HD, hemodialysis; HDF, hemodiafiltration.

The aim of the study is to investigate whether phosphate control improves after 6 months of treatment with HDF compared with conventional HD with similar dialysis frequency and session length.

Online HDF 3*4 h 5-6*3 h

n=5, 4-41 month of intensified HDF

Weekly Kt/V urea:	4.2	→	9.1
nPCR (g/kg)	1.28	→	1.43
Serum phosphate (mmol/l)	2.03	→	1.39
Serum ß2 microglobulin (mg/l)	27.5	→	24.1
Serum homocysteine (µmol/l)	21.6	→	13.4

Fischbach 2005

Why Does HDF Provide Adequate Phosphate Control?

Phosphate Kinetics During HDF

1. Increase the clearance of medium-sized moles

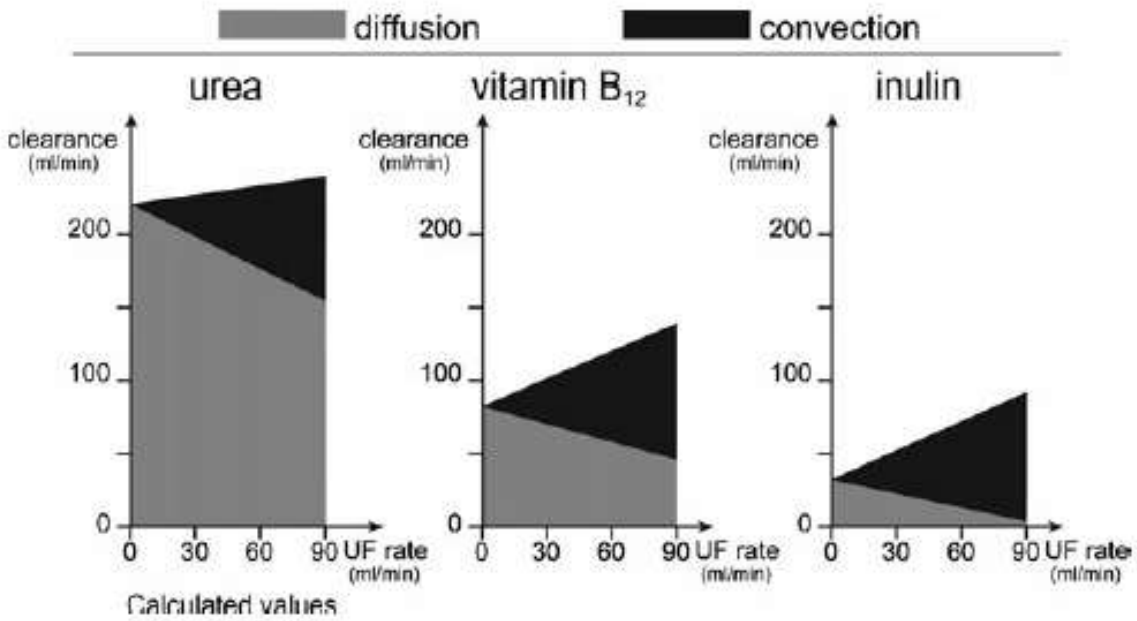


Fig. 2. Clearance in postdilution HDF for urea (MW = 60), vitamin B_{12} (MW = 1 355) and inulin (MW = 5 000) illustrating the impact of increasing convection (dark areas) on diffusion (light areas) at a blood flow rate of 300 ml/min and increasing ultrafiltration rate. Reprinted from [14] with permission.

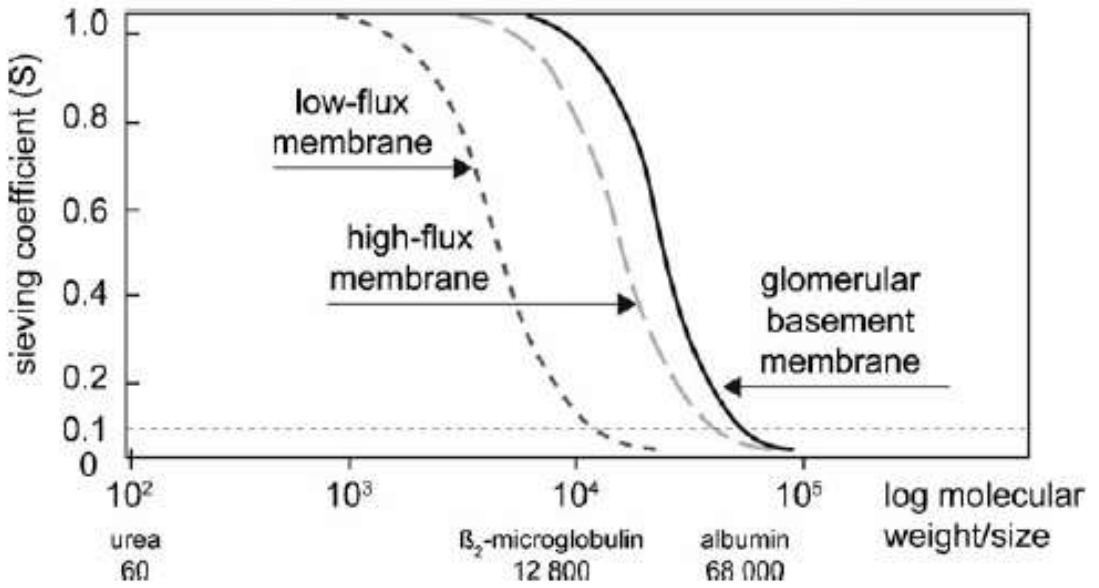
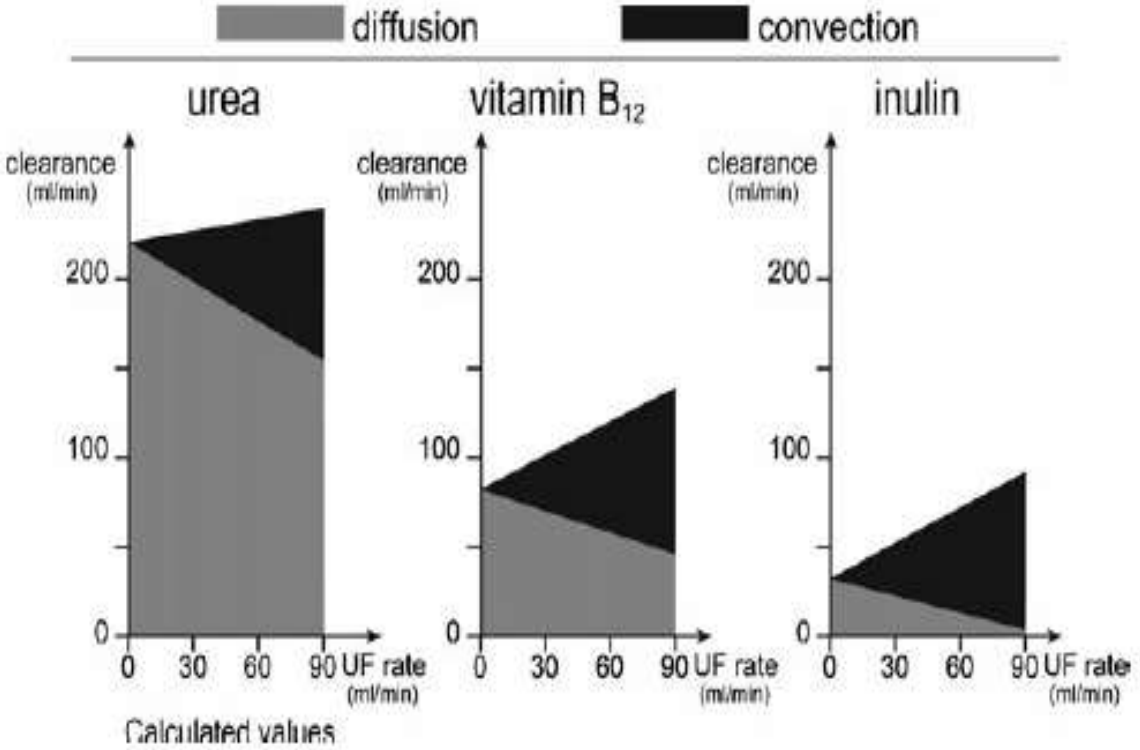


Fig. 1. Sieving curves for low-flux and high-flux dialysis membranes and human glomerular basement membrane. The molecular size for which the sieving coefficient = 0.1 is the cut-off of the membrane.

Phosphate Kinetics During HDF

2. Increased the clearance of large-sized moles



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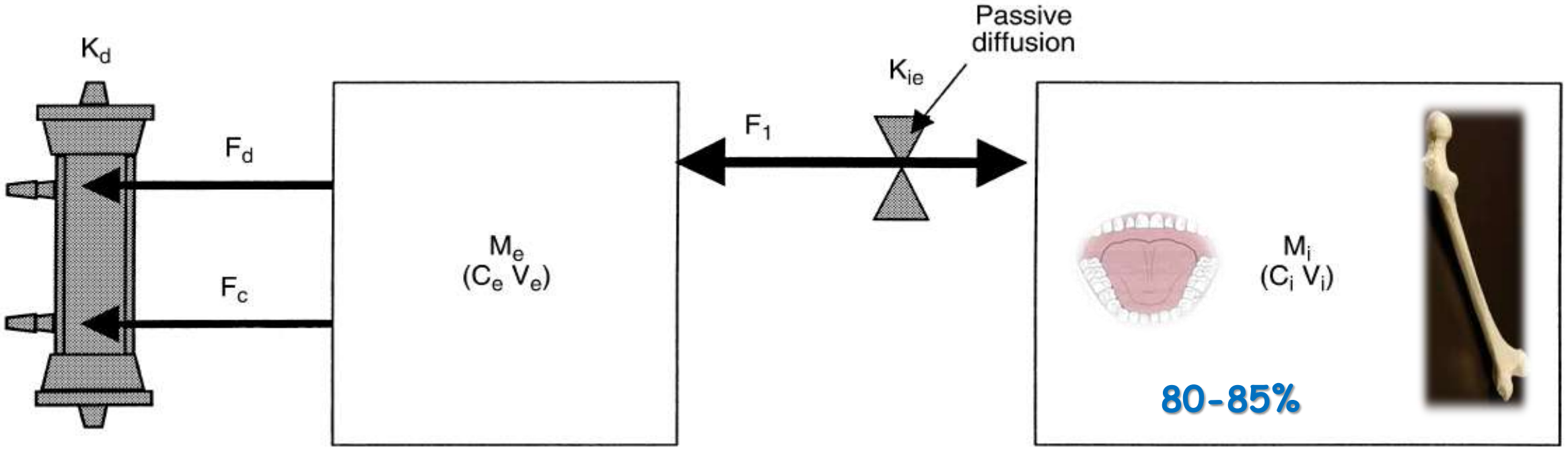
Alteration of key peptides and proteins involved in phosphate regulation, with some reports claiming increased clearance of PTH with hemodiafiltration.

Phosphate Kinetics During HDF

3. Multicompartmental distribution and kinetic behavior



Phosphate Kinetics During HDF

4. Improvement of the anti-inflammatory conditions

- Removing the cytokines harmful to bone metabolism.
- Thanks to the use of ultrapure endogenous infusate induces a deceleration in bone turnover due to 2PHT.


HD
HDF

The Cost of HDF

هتكلفنا كتير خبيبى

The Cost of HDF

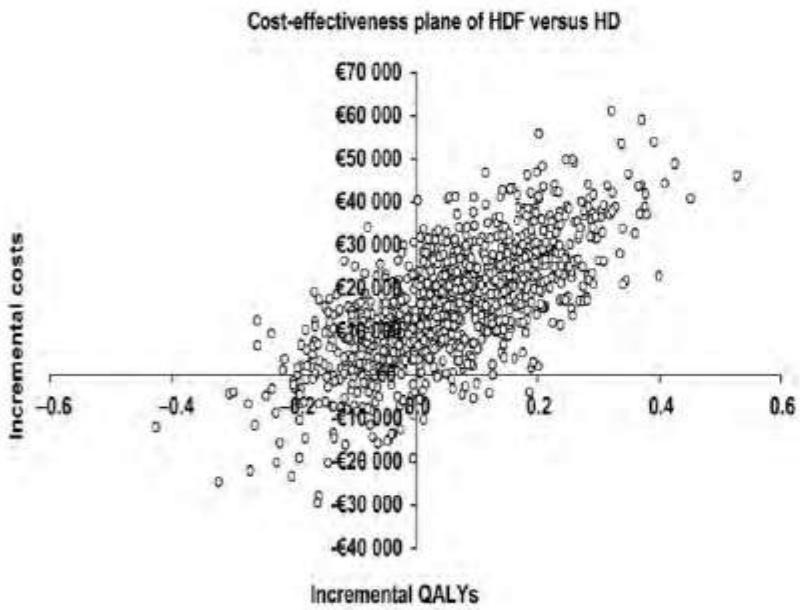


FIGURE 1: Cost-effectiveness plane of HDF versus HD. This figure shows the cost-utility of HDF versus HD as modelled with 1000 bootstrap replicates for 1000 patients aged 45–65 over a 5 year time period. Each dot represents the average for 1000 patients. Whereas sometimes HDF is both cheaper and less effective than HD (the dots in the left lower quadrant), most often HDF is more expensive and more effective (the dots in the right upper quadrant). HDF: haemodiafiltration; HD: haemodialysis; QALY: quality-adjusted life year.

Table 3: HDF and HD: modelled costs, QALYs and survival over 5 years

	Haemodiafiltration	Haemodialysis	Haemodiafiltration versus haemodialysis
Costs (€)	283 931 (264 500–303 187)	267 543 (248 294–286 157)	16 388 (–10 242–43 010)
QALYs	2.40 (2.22–2.59)	2.34 (2.17–2.53)	0.06 (–0.19–0.32)
Life years	3.43 (3.21–3.65)	3.35 (3.12–3.56)	0.08 (–0.22–0.39)

Depicted are means with 95% confidence intervals based on a patient aged 45–65.
The third column shows the incremental cost and effectiveness of HDF versus HD.
QALY: quality-adjusted life year.

1869

- HDF is not a more cost-effective option to treat ESRD patients than HD. Although the additional costs of HDF were limited, they were not compensated for by its marginal positive effect on utility. HDF could become cost-effective when its incremental costs, compared with HD, will be lowered to a maximum of €960.

Our Experience

20/8/2014

Effect of HDF on Serum Ca and P

	HD		HDF		P
	Median	Range	Median	Range	
Ca1	8.5	6-11.8	9	7-11	NS
Ca3	8.2	5.7-10	8.8	7-11	NS
Ca6	8.1	6.3-11.3	8.8	6-10.4	NS
P1	6.1	3-9	6.25	4.5-11	NS
P3	7	5-11	5.2	2.5-10.7	0.05
P6	7.8	5-13.7	4.8	2.9-8	<0.0001

20 patients


Thank You